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(21) International Application Number: PCT/US97/19276 (22) International Filing Date: 22 October 1997 (22.10.97) (30) Priority Data: 60/029,312 25 October 1996 (25.10.96) US (71) Applicant (for all designated States except US): ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): CONROW, Raymond, E. [US/US]; 1008 Colina Vista Lane, Crowley, TX 76036 (US). (74) Agents: RYAN, Patrick, M. et al.; Alcon Laboratories, Inc., Patent Dept., Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: METHOD OF PREPARING 21-ALKYLATED PREGNA-1,4,16-TRIEN-3,20-DIONES (57) Abstract Methods for preparing intermediates for 21-alkylated corticosteroids are disclosed. Pregna-1,4,16-trien-3,20-diones are contacted with a base and an alkylating agent to produce corresponding 21-alkylated pregna-1,4,16-trien-3,20-diones.		

REFERENCE: AJ
ZALIPSKY et al., USSN: 10/789,489
Atty. Docket No.: ALZ5015 R1/3222

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METHOD OF PREPARING 21-ALKYLATED PREGNA-1,4,16-TRIEN-3,20-DIONES

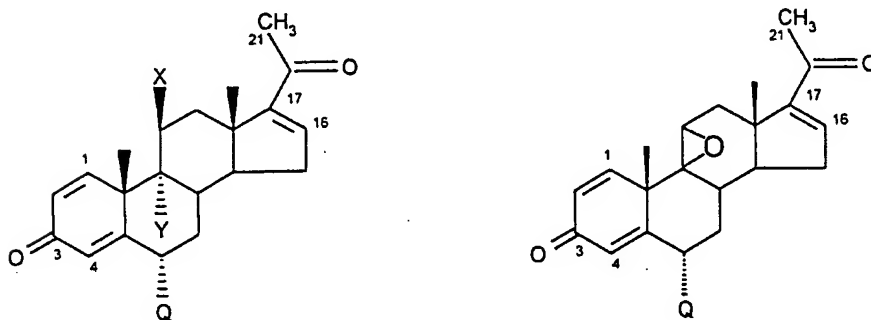
FIELD OF THE INVENTION

The present invention relates to methods of synthesizing intermediates which are used to prepare pharmaceutically active steroids. In particular, the present invention relates to methods of preparing 21-alkylated preгна-1,4,16-

trien-3,20-diones.

BACKGROUND OF THE INVENTION

Pregna-1,4,16-trien-3,20-diones of Formula I can be obtained using methods known in the art, for example, methods described in U.S. Patent Nos. 2,874,172; 3,033,873; 3,082,219; 3,281,415; 3,842,105; 4,012,510; and 4,216,159; Vitali et al., Gazz. Chem. Ital., 96:1115 (1966); Hofmeister et al., Chem. Ber., 109: 185 (1976) and Kovendi et al., Rev. Chim. (Bucharest), 27:467 (1976).



wherein X is $\text{OSiR}^3\text{R}^4\text{R}^5$ or $\text{OC}(=\text{O})\text{R}^6$;

R^3 , R^4 , and R^5 are independently C_1 - C_4 alkyl;

R^6 is H or C_1 - C_4 alkyl;

Y is H, F, or Cl; or X and Y taken together are a covalent bond; and

Q is H or CH_3 .

These pregna-1,4,16-trien-3,20-diones are useful for making pharmaceutically valuable corticosteroids.

U.S. Patent Nos. 3,947,478 and 3,862,194 disclose the preparation of pharmaceutically valuable 21-alkylated corticosteroids starting with a 16-pregnen-20-one in which the oxygen functional group at carbon 3 is present in the form of a ketal, enol ether, or protected hydroxyl group. Functional groups are then appended at positions 16 and 17. In a subsequent step, the 21-alkyl group is introduced by, for example, Mannich condensation or ketone alkylation reactions. The 3-keto group is unmasked at a later stage in the synthesis.

Alternative methods of preparing 21-alkylated corticosteroids are desired.

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SUMMARY OF THE INVENTION

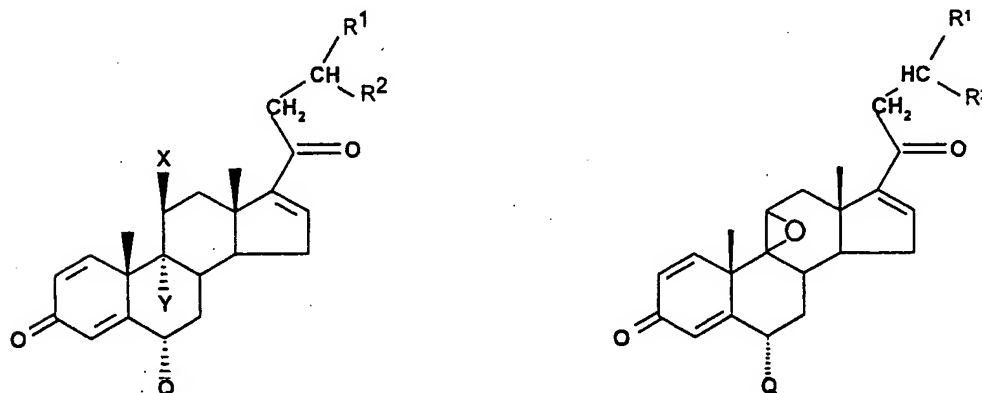
According to the present invention, pregna-1,4,16-trien-3,20-diones are contacted with a base and an alkylating agent in a ketone alkylation reaction to produce corresponding 21-alkylated pregna-1,4,16-trien-3,20-diones. The 21-alkylated products can be converted into pharmaceutically valuable 21-alkylated corticosteroids using techniques known in the art.

Among other factors, the present invention is based upon the finding that 21-alkylated pregna-1,4,16-trien-3,20-dione intermediates can be readily obtained from pregna-1,4,16-trien-3,20-diones, providing convenient access to pharmaceutically valuable 21-alkylated corticosteroids.

Among other factors, the present invention is also based upon the finding that certain ketone alkylation reactions are highly selective for the 16-en-20-one grouping in the presence of a 1,4-dien-3-one grouping.

DETAILED DESCRIPTION OF THE INVENTION

Ketone alkylation reactions are known in the art. For a discussion of the general chemical methodology employed in such reactions, see d'Angelo, Tetrahedron, 32:2979 (1976). According to the methods of the present invention, ketone alkylation reactions are used to convert pregna-1,4,16-trien-3,20-diones of Formula I above into the corresponding 21-alkylated pregna-1,4,16-trien-3,20-diones of Formula II below.



wherein R^1 and R^2 are independently H or $C_1 - C_4$ alkyl (optionally unsaturated);

X is $OSiR^3R^4R^5$ or $OC(=O)R^6$;

R^3 , R^4 , and R^5 are independently $C_1 - C_4$ alkyl;

R^6 is H or $C_1 - C_4$ alkyl;

Y is H, F, or Cl; or X and Y taken together are a covalent bond; and

Q is H or CH_3 .

Preferred compounds of Formula II are those where R^1 , R^2 , Y, and Q are H; X is $OSiR^3R^4R^5$; and R^3 , R^4 , and R^5 are CH_3 .

According to the present invention, a compound of Formula I is dissolved in a suitable solvent. Suitable solvents generally include, but are not limited to, tetrahydrofuran (THF), glyme, hexamethylphosphoramide (HMPA), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), diethyl ether, methyl t-butyl ether, and combinations thereof. Generally, it is desirable to cool the solution to increase the yield of the intended alkylated product. Appropriate temperatures will be determined by those skilled in the art, but will typically range from 0 to -100 °C. In most instances, it is expected that temperatures ranging from -20 to -80 °C will be sufficient for the ketone .
alkylation reaction to selectively produce the intended product.

Once the solution of the compound of Formula I reaches the chosen temperature, approximately one molar equivalent of base is added. Though other ratios of base to the compound of Formula I could be employed, they are generally not desirable. If an excess of base is used, the chances for side reactions are increased. (An excess of base can form the extended enolate of the A-ring dienone; see Barton et al., J. Chem. Soc., Perkin Trans. I, p. 1075 (1977) and Barton et al., Chem. Comm., p. 1497 (1969)). On the other hand, if less than one equivalent of base is used, the yield is limited. Suitable bases include lithium diethylamide; lithium diisopropylamide; lithium dicyclohexylamide; lithium isopropylcyclohexylamide; lithium 2,2,6,6-tetramethylpiperidide; lithium hexamethyldisilazide; sodium hexamethyldisilazide; and potassium hexamethyldisilazide. The preferred base is lithium hexamethyldisilazide.

After approximately one equivalent of base has been added to the cooled solution of the compound of Formula I, at least one equivalent of an alkylating agent is added. Suitable alkylating agents are those having the formula R^1R^2CHZ , wherein R^1 and R^2 are as defined above; and Z is selected from the group consisting of Br, Cl, and I. Z is preferably Br or I. As one skilled in the art will readily appreciate, it may be necessary or desirable to

allow the reaction temperature to increase after adding the alkylating agent in order to improve the yield.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLE 1

Preparation of Pregna-1,4,16-trien-11 β -ol-3,20-dione.

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a) The method of Kovendi et al., Rev. Chim. (Bucharest), 27:467 (1976) was modified. Semicarbazide hydrochloride (7.1 mL of a 5% aq. solution, 3.2 mmol) was added to a stirred, 50 °C solution of 21-deoxyprednisolone (1.82 g, 5.29 mmol) [see U.S. Patent No. 3,033,873 and Vitali et al., Gazz. Chim. Ital., 96:1115 (1966)] in acetic acid (60 mL) under Ar. The solution was heated to 75-80 °C (internal). After 2.7 h, another 4.7 mL of 5% aq. semicarbazide hydrochloride (2.1 mmol) was added. After 5.5 h at 75 °C, water (50 mL) was added and the solution was heated to 75 °C for 10 h and then to 90 °C for 1.5 h. The solution was cooled to room temperature, poured into 600 mL of water, stirred for 1 h, diluted with water to 1 L, stirred for 0.5 h and filtered on a fritted Buchner funnel. The solid was dried at 80 °C for 3-4 h to a constant weight of 1.00 g (58%, nominal) of crude product, C₂₁H₂₆O₃.

Proton NMR (CDCl₃): d 1.22 (s, 3H, 18-H₃); 1.48 (s, 3H, 19-H₃), 2.27 (s, 3H, 21-H₃); 1.0-2.7 (m, 12H); 4.38 (br q, 1H, J=2.5, H-11); 6.00 (s, 1H, H-4); 6.25 (dd, 1H, J=10 and 2, H-2); 6.66 (q, 1H, J=2, H-16); 7.32 (d, 1H, J=10, H-1).

This material was converted in 75% yield to the known trimethylsilyl derivative, 11 β -(trimethylsiloxy)-pregna-1,4,16-trien-3,20-dione (Formula I where X = OSi(CH₃)₃; Y = Q = H), as described in U.S. Patent No. 4,012, 510.

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b) The method of Kovendi et al., Rev. Chim. (Bucharest), 27:467 (1976) was modified. Semicarbazide hydrochloride (4.75 mL of a 5.0 % aq. solution, 2.14 mmol) was added to a stirred solution of 21-deoxyprednisolone (2.15 g, 6.25 mmol) [see U.S. Patent No. 3,033,873 and Vitali et al., Gazz. Chim. Ital., 96:1115 (1966)] in acetic acid (72 mL) under Ar. The solution was heated to 80-85 °C (bath) for 4.2 h. Water (75 mL) was added and heating (85 °C bath) was continued for 5.5 h. The solution was cooled to 23 °C over 11 h, poured into water (850 mL), cooled in ice (to 7 °C) and filtered on a fritted Büchner funnel. The solid was dried under vacuum to give 1.40 g (69%, nominal) of crude product, C₂₁H₂₆O₃.

Proton NMR (CDCl₃): δ 1.22 (s, 3H, 18-H₃); 1.48 (s, 3H, 19-H₃), 2.27 (s, 3H, 21-H₃); 1.0-2.7 (m, 12H); 4.38 (br q, 1H, J=2.5, H-11); 6.00 (s, 1H, H-4); 6.25 (dd, 1H, J=10 and 2, H-2); 6.66 (q, 1H, J=2, H-16); 7.32 (d, 1H, J=10, H-1).

This material was converted in 83% yield to the known trimethylsilyl derivative, 11β-(trimethylsiloxy)-pregna-1,4,16-trien-3,20-dione (Formula I where X = OSi(CH₃)₃; Y = Q = H), as described in U.S. Patent No. 4,012, 510.

EXAMPLE 2

Preparation of 21-Methyl-11β-(trimethylsiloxy)-pregna-1,4,16-trien-3,20-dione.

Lithium hexamethyldisilazide (estimated 0.9 M in THF, 2.1 mL, 1.9 mmol) was added over 8 min. to a stirred, cooled (-60 to -65 °C internal) solution of 11β-(trimethylsiloxy)-pregna-1,4,16-trien-3,20-dione (0.73 g, 1.83 mmol) in THF (12.0 mL) and HMPA (3.0 mL) under Ar. After a further 2 min, the cloudy pale-orange mixture was quenched rapidly with iodomethane (2.5 mL, 40 mmol) whereupon the temperature rose to -57 °C and the suspension cleared. The solution was warmed over 2 min to 10 °C, quenched with sat. KH₂PO₄, and partitioned with EtOAc. The organic solution was dried

(MgSO₄), filtered and concentrated. The residue (1.9 g) was purified by chromatography (80 g silica, 25% to 50% EtOAc-hexanes) to give 0.62 g (82%) of the product, C₂₅H₃₆O₃Si, as an off-white solid, m.p. 178 - 182 °C (dec.).

$[\alpha]_D^{23} + 144^\circ$ (c = 0.05, CHCl₃).

IR(KBr) 1660, 1060, 840 cm⁻¹.

Anal. calcd: C, 72.76, H, 8.79. Found: C, 72.57, H, 8.73.

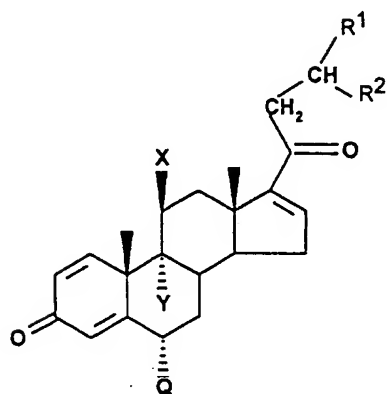
MS (CI, Me₃CH): 413 (m+1)(100), 323 ((m-Me₃SiOH)+1)(10).

Proton NMR (CDCl₃): d 0.24 (s, 9H, Me₃Si); 1.05 (t, 3H, J=7.3, Me-21); 1.18 (s, 3H, 18-H₃); 1.41 (s, 3H, 19-H₃); 1.0 - 2.8 (m, 11H); 2.6 (q, 2H, 21-H₂); 4.37 (br q, 1H, J=2.5, H-11); 5.99 (s, 1H, H-4); 6.25 (dd, 1H, J=10 and 2, H-2); 6.64 (q, 1H, J=2, H-16); 7.12 (d, 1H, J=10, H-1).

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

WHAT IS CLAIMED IS:

1. A method of preparing a compound of the formula



wherein R^1 and R^2 are independently H or $C_1 - C_4$ alkyl (optionally unsaturated);

X is $OSiR^3R^4R^5$ or $OC(=O)R^6$;

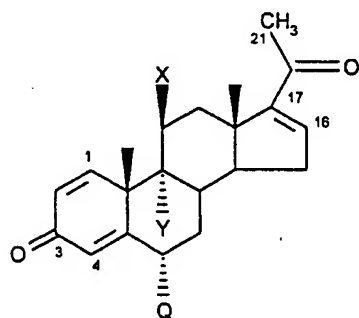
R^3 , R^4 , and R^5 are independently $C_1 - C_4$ alkyl;

R^6 is H or $C_1 - C_4$ alkyl;

Y is H, F, or Cl; or X and Y taken together are a covalent bond; and

Q is H or CH_3 ;

comprising dissolving a compound of the formula



wherein X, Y, and Q are as defined above,

in a solvent to form a solution and contacting the solution with a base and an alkylating agent.

5 2. The method of Claim 1 wherein the base is selected from the group consisting of lithium diethylamide; lithium diisopropylamide; lithium dicyclohexylamide; lithium isopropylcyclohexylamide; lithium 2,2,6,6-tetramethylpiperidide; lithium hexamethyldisilazide; sodium hexamethyldisilazide; and potassium hexamethyldisilazide.

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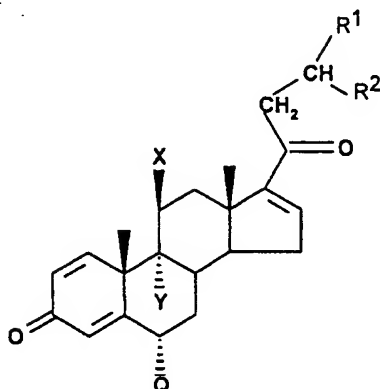
3. The method of Claim 2 wherein the base is lithium hexamethyldisilazide.

4. The method of Claim 1 wherein the alkylating agent has the formula
15 R^1R^2CHZ , wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and $C_1 - C_4$ alkyl (optionally unsaturated); and Z is selected from the group consisting of Br, Cl, and I:

5. The method of Claim 4 wherein R^1 and R^2 are H; and Z is selected
20 from the group consisting of Br and I.

6. The method of Claim 1 wherein the solvent is selected from the group consisting of tetrahydrofuran; glyme; hexamethylphosphoramide; 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; diethyl ether; methyl t-butyl
25 ether; and combinations thereof.

7. A method of preparing a compound of the formula



wherein R^1 and R^2 are independently H or $C_1 - C_4$ alkyl (optionally unsaturated);

X is $OSiR^3R^4R^5$ or $OC(=O)R^6$;

R^3 , R^4 , and R^5 are independently $C_1 - C_4$ alkyl;

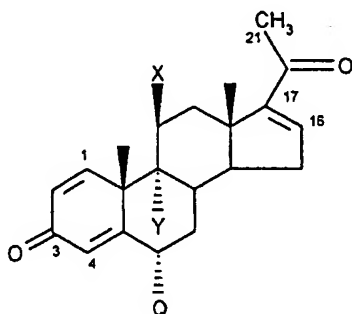
R^6 is H or $C_1 - C_4$ alkyl;

Y is H, F, or Cl; or X and Y taken together are a covalent bond; and

Q is H or CH_3 ;

comprising

a) dissolving a compound of the formula



wherein X, Y and Q are as defined above,

in a solvent to obtain a solution;

- b) cooling the solution of step (a) to a temperature from about 0 to about -100 °C;
- c) adding approximately one equivalent of a base selected from the group consisting of lithium diethylamide; lithium diisopropylamide; lithium dicyclohexylamide; lithium isopropylcyclohexylamide; lithium 2,2,6,6-tetramethylpiperidide; lithium hexamethyldisilazide; sodium hexamethyldisilazide; and potassium hexamethyldisilazide to the cooled solution of step (b); and
- d) adding at least one equivalent of an alkylating agent of the formula R^1R^2CHZ , wherein R^1 and R^2 are as defined above; and Z is selected from the group consisting of Br, Cl, and I to the solution of step (c).

8. The method of Claim 7 wherein R^1 , R^2 , Y, and Q are H; X is $OSiR^3R^4R^5$; and R^3 , R^4 , and R^5 are CH_3 .

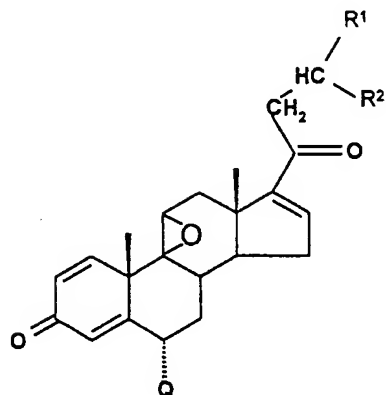
9. The method of Claim 7 wherein the base is lithium hexamethyldisilazide.

10. The method of Claim 7 wherein R^1 and R^2 are H; and Z is selected from the group consisting of Br and I.

11. The method of Claim 7 wherein the solvent is selected from the group consisting of tetrahydrofuran; glyme; hexamethylphosphoramide; 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; diethyl ether; methyl t-butyl ether; and combinations thereof.

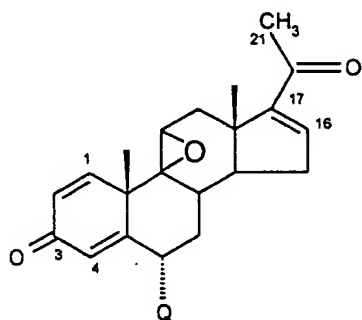
12. The method of Claim 7 wherein the solution of step (a) is cooled to a temperature ranging from about -20 to about -80 °C in step (b).

13. A method of preparing a compound of the formula



wherein R^1 and R^2 are independently H or $C_1 - C_4$ alkyl (optionally unsaturated); and Q is H or CH_3 ;

comprising dissolving a compound of the formula



wherein Q is as defined above,

in a solvent to form a solution and contacting the solution with a base and an alkylating agent.

14. The method of Claim 13 wherein the base is selected from the group consisting of lithium diethylamide; lithium diisopropylamide; lithium dicyclohexylamide; lithium isopropylcyclohexylamide; lithium 2,2,6,6-tetramethylpiperidide; lithium hexamethyldisilazide; sodium hexamethyldisilazide; and potassium hexamethyldisilazide.

15. The method of Claim 13 wherein the alkylating agent has the formula R^1R^2CHZ , wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and $C_1 - C_4$ alkyl (optionally unsaturated); and Z is selected from the group consisting of Br, Cl, and I.

16. The method of Claim 13 wherein the solvent is selected from the group consisting of tetrahydrofuran; glyme; hexamethylphosphoramide; 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; diethyl ether; methyl t-butyl ether; and combinations thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/19276

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J13/00 C07J51/00 C07J71/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. CAIRNS ET AL: "Alkylated Steroids. Part 3. The 21-Alkylation of 20-Oxopregnanes and Synthesis of a Novel Anti-inflammatory 16.alpha.,17.alpha.,21-Trimethyl Steroid (Org 6216)" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1., no. 8, 1981, LETCHWORTH GB, pages 2306-2316, XP002053903	1-16
Y	see page 2311, column 2, last paragraph see page 2306, column 2, paragraph 3	1-16
Y	DE 23 01 317 A (AKZO NV) 26 July 1973 see example 19	1-16
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

29 January 1998

Date of mailing of the international search report

13/02/1998

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/19276

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ²	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	M. J. WEISS ET AL: "The Formation of Steroid Enolate Anions by Reductive Procedures" TETRAHEDRON., vol. 20, no. 2, February 1964, OXFORD GB, pages 357-372, XP002053904 see page 367, last paragraph -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/19276

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